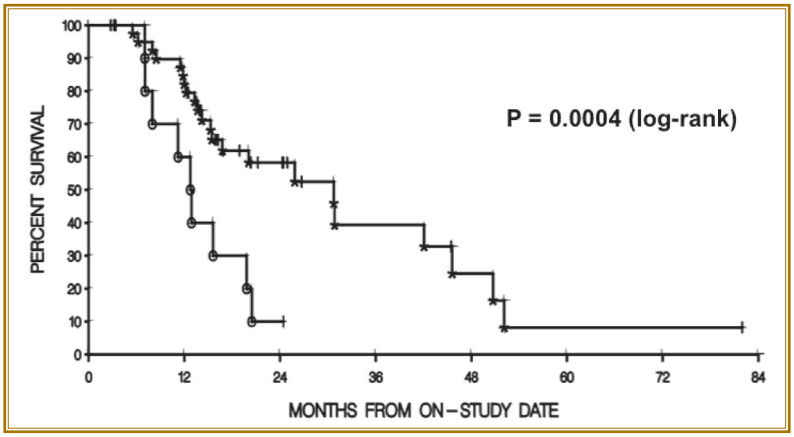
Genomic Marker Better Informs Treatment Choices for CRPC

Docetaxel remains the frontline standard of care for castration-resistant prostate cancer (CRPC), which grows without stimulation from male hormones. However, patient responses to this drug are highly variable. Researchers at CCR can now search a patient's genome for a specific genomic variant (called a polymorphism) that predicts lesser responses to docetaxel among CRPC patients.

Led by William Douglas Figg, Sr., Pharm.D., a Senior Investigator in CCR's Medical Oncology Branch, and Staff Scientist, Tristan Sissung, Ph.D., from the Pharmacogenetics Core of the Clinical Pharmacology Program, the clinical team studied a commonly inherited polymorphism in the *cytochrome P450 1B1 (CYP1B1)* gene. Specifically, the 432ValVal polymorphism in *CYP1B 9* (called the *CYP1B1*3* polymorphism) was shown to reduce a patient's survival following docetaxel treatment by more than half—from 30.6 to 12.8 months in combination trials, and from 15.3 to 7.5 months in trials that compared docetaxel alone to prednisone alone. Figg and colleagues conclude that testing for *CYP1B1*3* should guide docetaxel treatment decisions in patients with CRPC, because it could spare many from taking a drug unlikely to help them. Similarly, *CYP1B1*3* testing could inform treatment decisions involving docetaxel and other therapies in breast, ovarian, and non-small cell lung cancers.

While examining the mechanism of action for docetaxel, which inhibits microtubule disassembly, Figg and his team noted that this drug was being metabolized similarly by cells whether or not they carried the *CYP1B1*3* variant, based upon clearance data, which was the same for the differing genotypes. They wanted to know what was occurring at the biochemical level. They knew that the CYP1B1 enzyme metabolizes endogenous steroids, including estrogen, so they looked at how estrogen metabolites interact with tubulin, which makes up microtubules. They found that the estrogen metabolite estradiol-3,4 quinone interferes with docetaxel's ability to promote tubulin formation and binds directly with docetaxel, creating a drug-estrogen adduct.



(Image: T. Sissung, CCR)

The *CYP1B1*3* genotype is a potential marker for poor prognosis for men with castration-resistant prostate cancer who received docetaxel-based therapy. Men carrying two copies of *CYP1B1*3* (o) had reduced survival times compared to patients carrying at least one copy of the wild-type gene (*).

Based on these findings, Figg and colleagues proposed that *CYP1B1*3* interferes with docetaxel therapy by boosting the production of a metabolite that displaces docetaxel from its target and by creating adducts with more limited potency than the drug itself. "Patients who harbor the variant make more estradiol-3,4 quinone, which may work against docetaxel efficacy, while patients who have the wild-type gene make less of it and respond better to the drug, " explains Sissung.

The frequency varies among racial and ethnic groups worldwide, with approximately 20 percent of the Caucasian population harboring the *CYP1B1*3* variant. "We want to limit the number of people who receive docetaxel without experiencing benefits from the treatment," said Figg.

Figg has now patented the use of *CYP1B1*3* genotyping in blood samples to mark patients unlikely to benefit from docetaxel treatment in CRPC. "We think this genetic marker has value, and we are willing to work with other groups to validate the findings prospectively," he said. "The goal is to make sure this test reaches the market so it can be used to improve treatment planning."

The technology is available for licensing through the NIH Office of Technology Transfer. In addition to licensing, it is also available for collaborative research opportunities with Figg.

To inquire about licensing the technology, please contact Sabarni Chatterjee, Ph.D., at chatterjeesa@mail.nih.gov.

To learn more about Dr. Figg's research, please visit his CCR Web site at http://ccr.cancer.gov/staff/staff.asp?name=figg.